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SENSITIZATION POTENTIAL OF TRIETHYLENEDIAMINE
IMPREGNATED CHARCOAL(U) ARMY ENVIRONMENTAL HYGIENE
AGENCY ABERDEEN PROVING GROUND MD L W METKER ET AL.

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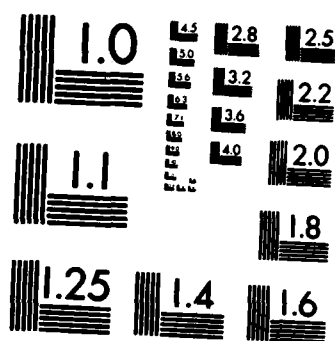
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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

INTERIM REPORT
SENSITIZATION POTENTIAL OF TRIETHYLENEDIAMINE
IMPREGNATED CHARCOAL
STUDY NO. 75-51-1124-83
JUNE 1982 - JUNE 1983

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Triethylenediamine was evaluated for its respiratory sensitization potential by means of inhalation exposures in male guinea pigs. A positive control, Toluenediisocyanate was used to demonstrate the validity of the test system. Additional testing is required but testing to date indicates that this material is not a respiratory sensitizer. ↑		



DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

Mr. Metker/jg/AUTOVON
584-3980

REPLY TO
ATTENTION OF

HSB-OT/WP

30 JUN 1983

SUBJECT: Interim Report, Sensitization Potential of Triethylenediamine
Impregnated Charcoal, Study No. 75-51-1124-83, June 1982 - June 1983

Commander
Chemical Systems Laboratory
Physical Protection Division
ATTN: DRDAR-CLW-CA/Mr. Conlisk
Aberdeen Proving Ground, MD 21010

EXECUTIVE SUMMARY

The purpose, essential findings and major recommendations of the inclosed report follow:

a. Purpose. The purpose of this study was to determine the sensitization potential of Triethylenediamine (TEDA) and estimate its safety as a charcoal impregnant in gas masks and other air purification systems.

b. Essential Findings. The material does not appear to be a respiratory sensitizer in the guinea pig under initial test conditions.

c. Major Recommendations. Require additional testing to further investigate the sensitization potential of this material. Studies are currently being designed to address existing data gaps.

FOR THE COMMANDER:

1 Incl
as (5 cy)

John C. Santos, COYMC
JOHN W. CUTTING, M.D.
Colonel, MC
Director, Occupational and
Environmental Health

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ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF

HSHB-OT/WP

INTERIM REPORT
SENSITIZATION POTENTIAL OF TRIETHYLENEDIAMINE
IMPREGNATED CHARCOAL
STUDY NO. 75-51-1124-83
JUNE 1982 - JUNE 1983

1. **AUTHORITY.** Letter, DRDAR-CLW-CA, subject: Sensitization Potential of TEDA Impregnated ASC Charcoal, with indorsements thereto, 15 April 1982.
2. **REFERENCES.** See Appendix for a listing of references.
3. **PURPOSE.** The purpose of this study was to determine the respiratory sensitization potential of triethylenediamine (TEDA) and estimate its safety as an impregnant for the ASC charcoal utilized in most respiratory protection devices.
4. **BACKGROUND.** Triethylenediamine has been suggested as a charcoal impregnant in respirator filter canisters to improve filter life against some agents and to reduce or eliminate the problem of ammonia off-gassing from the charcoal. Literature searches^{1,2} and commercial product information from several manufacturers (reference 4 and 5, Appendix) allude to this material being a possible respiratory sensitizer. The current data base for TEDA is insufficient to determine the safety of this material, however, available data concerning similiar aliphatic diamine catalysts indicate that they are sensitizers by both dermal and respiratory routes. Prior data (reference 4, Appendix) indicates that the material does not present a toxic hazard by the routes of administration tested. The material is neither a primary eye nor primary skin irritant as defined by 16 CFR 1500.41. Basic toxicity derived from the literature follows:

Acute Oral LD₅₀ = 700 mg/kg (rats)
Acute Dermal LD₅₀ = >2000 mg/kg (rabbits)
Acute LC₅₀ = >4 mg/l (rats)

Saturated vapor exposures caused no lethality and skin absorption studies indicated that the material was absorbed to only a minor degree.

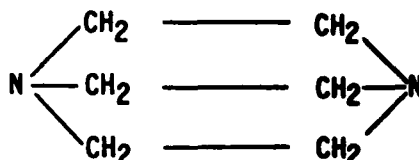
Use of trademarked names does not imply endorsement by the US Army but is intended only to assist in identification of a specific product.

¹ Tsonevski, D., A. Banjnova, S. Nesheva, and R. Nankova, "Modern Polyurethane Production," KHIG ZDRAVEOPAZ; 22(3), pp 267-273 (1979). Institute of Hygiene and Occupational Diseases, Sophia Bulgaria.
² Smith, D. B., and R. Henderson, "TDI Vapor Concentrations," Journal of Occupational Medicine, 17:413 (1975).

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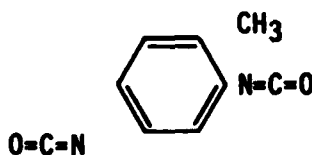
5. MATERIALS AND METHODS.*

a. The TEDA used in this study was a sample with a stated purity of 99.984 percent provided by Air Products and Chemical Inc., Allentown, PA 18105. The material was identified by Lot No. 210-H-2-01 and its structural formula is shown below.

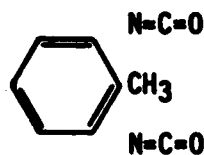


It was a white hygroscopic crystal with a molecular weight of 112.17, a melting point 158°C, a boiling point 174°C, and sublimed readily at room temperature.

b. The positive control used in this study was Toluene Diisocyanate (TDI). It was supplied under the commercial tradename of Mondur TD-80® with a stated purity of 99.96 percent. The material was supplied by the Hercules Company Inc., Wilmington, Delaware, and identified as Lot No. E-002-2000-2-620. It was selected because of its proven industrial history as a potent respiratory sensitizer. The structural formulae of the two isomeric forms of the material are shown below.



2,4 isomer



2,6 isomer

* The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. This report and data generated in this study are stored in Toxicology's file located in Room 3011, Building E2100, APG-EA, MD 21010.
● Mondur TD-80 is a registered trademark of the Hercules Chemical Company, Inc., Wilmington, Delaware.

c. Test Procedures.[†]

(1) Test Species. Male Hartley Guinea Pigs were purchased from Hazelton Dutchland Laboratories, Inc., Denver, Pennsylvania. Issue weight ranged from 250-300 gm and all animals were identified by ear tattoo. Five animals were housed in each stainless steel cage with food and water available ad libitum (reference 2, Appendix).

(2) Respiratory Sensitization Studies. The initial study run in this series attempted to produce a respiratory sensitization reaction that could be quantified and serve as a positive control of the test system's validity. The TDI was chosen as the positive control due to its proven capacity to induce respiratory sensitization reactions in both guinea pigs and human populations.^{3,4} Twenty guinea pigs were randomly selected and divided into treatment and control groups. To prevent possible contamination of the laboratory area, the animals were housed in stainless steel cages inside two 2000-liter inhalation chambers. The animals were removed for daily exposures or experimental procedures only and were kept in these chambers for the duration of the test. Actual exposures were conducted as follows: The guinea pigs were placed in individually compartmented stainless steel cages and placed in a 200 L dynamic exposure chamber. Chamber airflow was approximately 0.5 M³/min. The TDI was dispersed from a standard gas washing bottle[‡] incorporating a fritted disc at the bottom (pore size 170-220 u). One ml of TDI was placed on the fritted disc and dried compressed nitrogen was passed through the disc at a rate of 1600 ml/min. The TDI vapors were passed into a round glass 2-liter mixing chamber and then into the inhalation chamber. Compound concentrations were determined by withdrawing 20-liter samples of chamber air through glass bubblers filled with 10 ml of an absorbing solution. The resultant mixture was then analyzed for TDI using a liquid chromatographic method (reference 6, Appendix). Exposures were conducted 6 hours per day, 5 days per week for 2 weeks. The animals were rested for 14 days and then challenged with a single 1-hour exposure at 1/10 the concentration of the sensitizing dose. The TEDA exposures were conducted in an identical fashion with the exception of the method of vapor generation. The TEDA crystals were packed in a glass column with alternating layers of glass beads. The column was held at 30°C with a heating tape which surrounded the glass column. Dried, purified nitrogen was passed through the tube at 1600 ml/min and the vapors were then mixed with room air entering the chamber inlet. Chamber air samples were collected in an absorber solution and analyzed using a gas chromatographic method.

[†] In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals." US Department of Health Education and Welfare Publication No. (NIH) 80-23, revised 1978.

³ Butcher, B. J., J. E. Solvaggio, H. Weill, and M. M. Zenskind, "Toluene Diisocyanate (TDI) Pulmonary Disease: Immunologic and Inhalation Challenge Studies," *Journal of Allergy and Clinical Immunology*, 58:89 (1976).

⁴ Karol, M. H., H. H. Ioset, E. J. Riley, and Y. C. Alarie, "Hapten-specific respiratory hypersensitivity in guinea pigs," *American Industrial Hygiene Journal* 39:546 (1978).

[‡] Corning glass works, Corning, New York.

6. RESULTS.

a. Dermal Study. An initial study was run with 20 male guinea pigs (10 treated and 10 controlled) in an attempt to develop a sensitization reaction by dermal application and then elicit a response by inhalation exposure. The positive control, 50 μ l of TDI, was applied to the shaved backs of the treated animals. Control animals received the same volume of toluene. The sensitization procedure was terminated after two applications resulted in severe dermal irritation. The animals were rested for 14 days and then challenged with a 1-hour, whole-body, inhalation exposure to TDI at 0.5 mg/m^3 . Four-hours postexposure, the animals were tested for pulmonary function. The parameters measured (rate, tidal volume, intrapleural pressure, compliance and resistance) were not significantly different between TDI and control animals. Since this procedure did not elicit a sensitization reaction in the positive control animals, it was not repeated with TEDA.

b. Intradermal Studies. Intradermal sensitization studies were run with both TDI and TEDA. Two groups of ten guinea pigs each were injected intradermally with 0.1 ml of a 0.1 percent solution of either TDI or TEDA. The animals received 10 injections of the material over a 3-week period, were rested for 2 weeks and then received the injected challenge dose (0.05 ml of a 0.1 percent solution of either TDI or TEDA) to determine if a dermal sensitization reaction could be produced. The TDI treated group exhibited a severe reaction and was classed as a strong sensitizer by this route of administration (reference 6, Appendix). By comparison, the TEDA treated animals exhibited no response and the material was considered a nonsensitizer by this route of administration.

c. Inhalation Study with TDI. To assess the validity of the test system, the first inhalation study was performed using TDI. Ten male guinea pigs were exposed to a concentration of 10 mg/M^3 , 6 hours per day, 5 days a week, for 2 weeks. The animals were rested for 2 weeks and then challenged with a single 1-hour inhalation exposure to the material at 1/10 the challenge dose to check for a sensitization reaction. To allow for a maximum response the animals were tested for pulmonary function starting at 4-hours postexposure. The results of this testing are shown in Table 1.

TABLE 1. INHALATION RESULTS WITH TDI (4-HOURS POSTEXPOSURE)

	Rate (resp/min)	Tidal Volume (mls)	Pressure (cm H ₂ O)	Compliance (l/cmH ₂ O/gm)	Resistance (cm/l/sec/gm)	Minute Volume (ml/min)
Controls	35.5 +10.8	2.26 +0.38	2.58 +0.90	3.53 +0.74	0.004 +0.004	77.5 +27.5
TDI exposed	55.0 +20.7	2.55 +0.57	4.00 +2.80	2.79* +0.89	0.004 +0.003	132.2* +38.6

* Significantly different from control at $p = 0.05$

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Pulmonary Compliance, the most significant parameter affected, showed the severe reduction that would be expected in a respiratory sensitization reaction. This statistically significant finding would seem to indicate that this test methodology was sufficient to screen materials of this type. Though not statistically significant, both rate and esophageal pressure increased markedly indicating a sensitization response. A contradictory finding was the lack of change in pulmonary resistance, however, an extremely large standard error may mask the effect. This may be related to the transducer used for measuring esophageal pressure. Pressures encountered in these experiments are at the extreme lower limit of sensitivity for this device and indicate that a more sensitive device will be required for future work. In an attempt to determine the duration of the respiratory sensitization response, the inhalation exposure was repeated with another group of 20 guinea pigs. The only change in the experimental procedure was to perform the pulmonary function testing at 7-hours postexposure. Results of this testing are shown in Table 2.

TABLE 2. INHALATION RESULTS WITH TDI (7-HOURS POSTEXPOSURE)

	Rate (resp/min)	Tidal Volume (mls)	Pressure (cmH ₂ O)	Compliance (l/cmH ₂ O/gm)	Resistance (cm/l/sec/gm)	Minute Volume (mls/min)
Controls	33.2 +15.3	3.17 +1.44	3.47 +1.20	3.56 +1.28	0.004 +0.002	89.3 +24.3
TDI exposed	33.9 +13.5	3.16 +1.00	3.89 +1.20	4.09 +1.25	0.003 +0.002	98.8 +23.4

As shown in the table above were no statistically significant changes in any of the parameters measured at 7-hours postexposure.

d. Inhalation Study with TEDA. Twenty male guinea pigs were utilized in this study. The experimental procedures were identical to the TDI study. The animals were exposed 6 hours a day, 5 days a week for 2 weeks to a concentration of 50 mg/M³ TEDA vapor. After a 2 week rest period the animals were challenged with a 1-hour exposure to a 5.0 mg/M³ TEDA concentration and tested for pulmonary functions at 7-hours postexposure. Results of these tests are shown in Table 3.

TABLE 3. INHALATION STUDY WITH TEDA (7-HOURS POSTEXPOSURE)

	Rate (resp/min)	Tidal Volume (mls)	Pressure (cmH ₂ O)	Compliance (l/cmH ₂ O/gm)	Resistance (cm/l/sec/gm)	Minute Volume (ml/min)
Controls	39.9 +13.1	3.97 +1.33	4.79 +2.14	3.07 +0.81	0.002 +0.001	150.0 +53.8
TEDA Exposed	34.6 +12.6	4.05 +2.07	3.63 +1.24	2.98 +0.90	0.002 +0.001	131.1 +30.0


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There were no statistically significant changes in any of the measured parameters at 7-hours postexposure.

7. CONCLUSIONS. Data generated from these studies indicate that TDI is a reasonably good positive control substance for dermal and inhalation sensitization. The sensitivity reaction elicited by TDI appears to peak at 4- to 6-hours postexposure. Studies performed to date indicate that under these test conditions TEDA is not a hazard as a respiratory or dermal sensitizer.

8. RECOMMENDATIONS. Require that further work be done on these materials, due to possible discrepancies in the onset, duration and severity of the respiratory sensitization reaction seen in the positive control procedures. Additional inhalation exposures to TEDA with emphasis on altering the postexposure time periods and using individual animals as their own controls by monitoring pulmonary function both before and after exposure are planned. Additionally, serological evaluation will be done with these animals to further substantiate potential allergic physiological changes encountered.


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MAJ, MC
Acting Chief, Toxicology Division

APPENDIX

REFERENCES

1. Title 16, Code of Federal Regulations (CFR), 1980 rev, Section 1500.41, Method of Testing Primary Irritant Substances.
2. Standing Operating Procedure (SOP), Animal Facilities, Toxicology Division, USA Environmental Hygiene Agency (USAEHA), 1982.
3. SOP, Guinea Pigs Sensitization Tests, Toxicology Division, USAEHA, 1981.
4. Material Safety Data Sheet, Air Products and Chemicals, Inc., P.O. Box 538, Allentown, Pennsylvania.
5. Chemical Hazard Identification Data Sheet, Dynamic Corporation, 11140 Rockville Pike, Rockville, Maryland.
6. HPLC Analysis of Toluene Diamine, Liquid Chromatographic Methods Manual, Organic Environmental Chemistry Division, Chromatographic Analysis Branch, USAEHA.

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